949,407

PATENT SPECIFICATION

NO DRAWINGS

949,407

Date of Application and filing Complete Specification Aug. 22, 1961.

No. 30192/61.

Application made in Germany (No. H40272IVb/12o) on Aug. 23, 1960.

Complete Specification Published Feb. 12, 1964.

Index at acceptance:—C2 U(4A1, 4B2, 4C9, 4X)

International Classification:—C 07 c

COMPLETE SPECIFICATION

Process for the Manufacture of Dihydroouabain

We, DR. HOMMEL'S CHEMISCHE WERKE UND HANDELSGESELLSCHAFT M.B.H., of Am Hauptbahnhof, Müllheim/Baden, Germany; a Joint Stock Company organised under the laws of Germany; do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to a process of manufacturing dihydroouabain.

Ouabain, which is also known as G-strophanthin, is a valuable resin-like glycoside which, however, constitutes a powerful poison when administered in too large a dose.

The dihydro derivative of ouabain, namely dihydroouabain *per se* is also known and was first prepared by Walter A. Jacobs and Alexander Hofmann, J. Biol. Chem. 74 (1927), page 787ff. These authors prepared the substance by the hydrogenation of ouabain in an aqueous solution in the presence of colloidal palladium. After precipitation with ammonium sulphate (by saturation of the aqueous solution, drying of the precipitate and extraction with ethanol) the dihydroouabain was recovered in an amorphous state from the concentrated solution by precipitation with a mixture of ether and petroleum ether. The literature gives its decomposition point as 105° C.

A dihydroouabain derivative so prepared has not been considered suitable as a therapeutic agent because of its fluctuating degree of effectiveness and comparitively low stability.

It has now been realised however that the substance so prepared and described as dihydroouabain is not a pure compound but is contaminated by a considerable quantity (as much as 5 to 10 per cent) of ethanol and by traces of ammonium sulphate. It has also now been found that it is possible to purify the impure dihydroouabain and that, when pure, dihydroouabain has a similar therapeutic effect to ouabain, albeit not as strong. It has, however, more than twice the therapeutical breadth of ouabain, so that administration of an overdose is not as dangerous when, at the like indication, dihydroouabain is given in lieu of ouabain. This means that the range of applicability of these important glycosides is thereby widened considerably.

It is an object of the present invention to provide a method of preparing dihydroouabain in a relatively pure state.

According to the present invention there is provided a process for the preparation of chemically pure dihydroouabain which comprises hydrogenating ouabain using a noble metal catalyst, isolating the hydrogenation product and extracting the dihydroouabain therefrom in such a manner that the dihydroouabain immediately prior to a vacuum drying step is contaminated only by a solvent, which, on drying *in vacuo*, completely volatilises and drying said contaminated dihydroouabain *in vacuo*.

The dihydroouabain in the isolated hydrogenation product may be extracted therefrom with said completely volatilisable solvent and precipitated from the resultant extract solution. Alternatively the dihydroouabain in the isolated hydrogenation product may be extracted therefrom by an extracting solvent other than the said completely volatilisable solvent, such as a hitherto described extracting solvent like ethanol, then precipitated from the resultant extract solution, re-dissolved in said completely volatilisable solvent and then re-precipitated from the resulting solution.

The preferred completely volatilisable solvent is methanol. The complete removal of this solvent can be accelerated by using adsorption—or absorption agents during vacuum drying.

The compound obtained according to the method of the invention has a melting point

[*Price* 4*s.* 6*d.*]

of 168—170° C, and a specific optical rotation at 20° C is −45.3° C (−1.0 D line in water). Its decomposition point is above 170° C.

The invention will now be further illustrated by the following Examples. However, it should be understood that these are given merely by way of explanation, not of limitation, and that numerous changes may be made in the details without departing from the spirit and the scope of the invention as hereinafter claimed.

EXAMPLE 1

5 g. ouabain were dissolved in 450 ml water and hydrogenated, after addition of 0.4 g. colloidal palladium. From the solution thus hydrogenated, the dihydroouabain obtained could either be recovered by precipitation with ammonium sulphate or by lyophilisation. The crude product obtained by either method was extracted with absolute methanol. The filtered extract was evaporated to dryness *in vacuo*, if necessary after decolourization with carbon black. During evaporation, care was taken to maintain the temperature at or below 20° C. The residue was dissolved in 5 ml absolute methanol, again filtered and precipitated with anhydrous ether. Additional dihydroouabain was recovered from the mother liquor by addition of petroleum ether. The substance was dried *in vacuo* over P_2O_5 and had a melting point of 168° C.

EXAMPLE 2

5 g. ouabain were treated as described in Example 1, but the ammonium sulphate precipitate, or the lyophilisation residue, respectively, was extracted with absolute ethanol in lieu of methanol. The extract then was treated as described in Example 1. The precipitation from methanol with ether and petroleum ether was repeated until the melting point of the product had reached 168° C.

WHAT WE CLAIM IS:—

1. A process for the preparation of chemically pure dihydroouabain which comprises hydrogenating ouabain using a noble metal catalyst, isolating the hydrogenation product and extracting the dihydroouabain therefrom in such a manner that the dihydroouabain immediately prior to a vacuum drying step is contaminated only by a solvent, which on drying *in vacuo* completely volatilises and drying said contaminated dihydroouabain *in vacuo*.

2. A process as claimed in Claim 1 in which the dihydroouabain in the isolated hydrogenation product is extracted therefrom with the said completely volatilisable solvent and precipitated from the resultant extract solution.

3. A process as claimed in Claim 1 in which the dihydroouabain in the isolated hydrogenation product is extracted therefrom by an extracting solvent other than the said completely volatilisable solvent, then precipitated from the resultant extract solution, re-dissolved in said completely volatilisable solvent and then re-precipitated from the resulting solution.

4. A process as claimed in Claim 3 in which said extracting solvent is ethanol.

5. A process as claimed in any of the preceding claims in which said completely volatilisable solvent is methanol.

6. A process as claimed in any of the Claims 2 to 4 in which the precipitating and/or reprecipitating agent is anhydrous ether or petroleum ether.

7. A process as claimed in any of the preceding claims in which the drying *in vacuo* is accelerated by the simultaneous use of adsorption or absorption agent.

8. A process for the preparation of chemically pure dihydroouabain as claimed in Claim 1 and substantially as herein described with reference to the Examples.

9. Dihydroouabain when prepared by the process claimed in any of the preceding claims.

10. Dihydroouabain with a melting point of 168 to 170° C, an optical specific rotation of −45.3 at 20° C and a decomposition point of above 170° C.

REGINALD W. BARKER & CO.,
Patent Agents for the Applicants,
13, Charterhouse Square, London, E.C.1.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1964.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.